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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/559,021	04/27/2000	Alexander V. Sokoloff	Mirus.014.02	1870

7590 02/10/2004

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	16

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

C.C.

Office Action Summary	Application No.	Applicant(s)	
	09/559,021	SOKOLOFF ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-16* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 2/15/2002, in which a replacement paper copy of the sequence listing, corresponding computer readable form and attorney's statement concerning the submission were filed. The application is now in sequence compliance.

Receipt is also acknowledged of an amendment, filed 8/3/2001, in which several of the claims were amended (claims 1-6, 8-11, 13-16). It is noted that the response was technically nonresponsive in that the marked up copy of the claims did not match exactly the clean copy of the claims. Upon review of the clean copy of the claims, the marked-up copy of the amended claims and the prosecution history, the examiner was able to determine which modifications were done to which claims. The clean version of the claims submitted 8/3/2001 was used for examination for each claim. In the future, it is requested that when applicants completely rewrite new claims, as was done for several of the pending claims, a completely new claim corresponding to the next claim number not already used in prosecution of the instant application be submitted instead. Further, applicants are reminded that the office has revised the amendment guidelines as of July 2003. Please see http://www.uspto.gov/web/patents/ifw/ for details.
Claims 1-16 are pending and under consideration in this application.

This action is not final as there are new grounds of rejection made herein that were not necessitated by applicants' amendment of the claims.

Response to Amendment

Any rejection of record in the previous office action not addressed herein is withdrawn. Applicants' arguments concerning the rejection of claims as being anticipated by Pasqualini et al

were persuasive. Specifically, the response argues that Pasqualini et al do not explicitly teach phage that are resistant to inactivation by injection into the blood stream. Rather, Pasqualini et al teach methods where so many phage are injected into the animal that the immune response is largely saturated and the phage that were recovered were merely ones that were not inactivated for this reason. Upon review of the Pasqualini et al reference, it is apparent that a relatively large number of phage (~10^{14} to 10^{16} phage) were injected into the test mice (i.e. 2 month old BalbC females), and that the mice were harvested almost immediately afterwards (~4 minutes post injection; e.g. see Figure 1 legend). Further, Pasqualini et al never couch the discussion of their results in terms of resistance to inactivation for the phage recovered in their selection methods. Their methods are directed to isolation of peptides responsible for targeting the phage to a particular host organ or tissue. Based upon applicants' results where larger animals (i.e. Sprague-Dawly rats) were injected with fewer phage (~10^{7}-10^{9} phage) and "rescue" of specific phage was accomplished only with an excess of UV-inactivated phage (10^{12} phage) displaying the same epitope (e.g. Table 4), it is reasonable to argue that the phage recovered by Pasqualini et al did not *necessarily* possess the inherent trait of being resistant to inactivation by some component of the blood. Therefore, because the inherency argument cannot be sustained, the rejection is withdrawn.

Ruoslahti et al (U.S. Patent No. 5,622,699A; see the entire patent) is cited as being relevant art to the instant claims. The '699 patent teaches much of the same approach taught by Pasqualini et al and is an extension of the same work. However, like the Pasqualini et al reference, it does not explicitly teach that the phage recovered in their methods are necessarily resistant to inactivation by any component of the blood.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 14-16 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. **This is a new rejection.**

Claims 14-16 comprise actual methods steps but appear to be directed to a composition (a "peptide"). Such claims, directed to a composition but also comprising methods steps are not proper claims as it cannot be determined if they are directed to a composition or a method. If applicants are attempting to claim a product by its process of manufacture, it would be remedial to amend the claim language to explicitly recite that the peptide is obtained by the process rather than including positive action steps in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 2 is drawn to a process for determining epitopes associated with specific parenchymal cells where an epitope display library of particles, sized to exit blood vessels and

contact parenchymal cells, is inserted into a blood vessel and exposed to the parenchymal cells and cell specific epitopes are identified. There is no literal support in the instant specification for the methodology recited in the rejected claim. Therefore, the rejected claim is impermissible NEW MATTER. **This is a new rejection.**

Claims 8-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection.**

The rejected claims are directed to a peptide for complexing with a drug to protect the drug from antibody inactivation during delivery comprising determining a phage coat peptide sequence from the phage selected by the method of claim 1 and associating the peptide with the drug to be delivered. The peptide can be present on a phage capsid. Claims 9 & 15 specify the peptide contains a carboxy terminal amino acid selected from the group consisting of arginine and lysine. Claim 16 recites that the peptide contains a tyrosine residue.

There is no literal support in the specification for the limitations of claims 9, 15 and 16 as relates to a peptide that prevents inactivation by an antibody. For example, the description of a peptide comprising a C-terminal arginine or lysine residue is directed to a peptide that confers resistance to complement inactivation, not inactivation by an epitope-specific antibody. Therefore, the subject matter of claims 15-16 is impermissible NEW MATTER.

Even if there were sufficient support for the specific limitations of claims 9 & 15-16, there is insufficient description provided by the instant specification for peptides identified by the methods of claim 1 that would confer protection on a given drug such that the drug is deliverable to a target cell. The instant specification teaches only a single type of peptide, those ending in an arginine and/or lysine residue that may provide some protection from complement inactivation in rats due to an ability to prevent binding of CRP (protein C reactive protein). No description is provided of even a single embodiment of the claimed invention where the peptide prevents inactivation by any antibody. No guidance is provided as to the further amino acid sequence/structure of the rest of the polypeptide. No further description is given concerning peptides identified in other contexts (e.g. displayed on the surface of T4 phage, M13 phage, etc.) and/or not possessing a C-terminal arginine or lysine residue.

Given that the instant claims encompass an incredibly large genus of polypeptides that might be identified by the methodology of claim 1, and given that the instant specification provides no reliable basis for the skilled artisan to envision specific embodiments of the claimed method, there would have been no means for the skilled artisan to envision a sufficient number of specific embodiments of the claimed invention to describe the broadly claimed genus of peptides. Therefore, the skilled artisan would reasonably have concluded applicants were not in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **The following rejections are maintained for reasons of record in the previous office action which are repeated below.**

Claim 10 recites the limitation that the peptide comprises "a clone 20-6 peptide". The metes and bounds of this term are unclear as it can be read to encompass any protein comprising any di-amino acid sequence found within applicants clone described as the "20-6 peptide" (see page 63, Table 3 of the instant specification, SEQ ID NOS: 61-62). It appears upon reading the specification that the claim may be intended to specify that the phage of claim 8 comprises "the" clone 20-6 fusion protein described by SEQ ID NO: 61. It would be remedial to amend the claim to read something like "...wherein the coat protein comprises the amino acid sequence of SEQ ID NO: 61."

Claim 11 is vague and indefinite in that the metes and bounds of the phrase "...determining phage coat peptide interactions with antibodies using the selected phage..." are unclear. It is unclear which interactions are to be determined or how these interactions are "determined". For example, the phrase can be read as specifying that the interaction amongst different coat protein peptides is determined. Alternatively, it can be read as reciting that the interaction of the phage coat peptide with antibodies is determined. Upon reading the specification, it appears the latter interpretation is correct. However, the phrase is still vague and indefinite in that it is unclear what interactions with antibodies are to be determined or how.

Response to Arguments/112 2nd Rejections

Applicant's arguments filed 8/3/2001 have been fully considered but they are not persuasive. The response asserts that the amendments to the claims obviate the outstanding rejections. However, the amendments to the claims presented in the response filed 9/3/2001 do not adequately address the remaining 112 2nd issues for claims 10-11.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 6-8, 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Merril et al (PNAS USA, Vol. 93, pages 3188-3192, April 1996; see the entire reference). **This is a new rejection.**

Merril et al teach methods for identifying phage (e.g. λ phage) comprising mutations in their coat proteins that allow the mutant phage to be resistant to inactivation in the blood of BALB/c mice (e.g. Abstract, Figure 1). In particular, two different selections were done that yielded phage (e.g. Argo1 and Argo2) comprising the same substitution of the basic amino acid lysine for glutamic acid at residue 158 of gpE, a major surface protein of the phage λ capsid (e.g.

page 3190, column 2). Phage Argo2 appears to also comprise a basic substitution in the major capsid protein, gpD. Merril et al teach that the phage isolated by their methods might be useful for the treatment of microbial infections and demonstrate this capacity in a mouse model for peritonitis (e.g. Figure 3).

The population of phage used in the methods taught by Merril et al can be considered as being a "phage display library" in the broad meaning that a plurality of different variants are put into a selection protocol that is dependent upon the ability of a variant to escape inactivation by the host organisms' defenses (e.g. the reticuloendothelium system) due to a different peptide sequence displayed on the capsid surface of the variant. It is noted that applicants have not specifically and explicitly defined what constitutes a "phage display library", so that a reasonably broad interpretation of the term such as that given above can be applied to the rejected claims.

Claims 1, 3, 6-8, 11, 13-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Merril et al (U.S. Patent No. 5,811,093A; see the entire patent). **This is a new rejection.**

Merril et al teach methods for identifying phage (λ phage) comprising mutations in their coat proteins that allow the mutant phage to be resistant to inactivation in the blood of BALB/c mice (e.g. Abstract, Figure 1). In particular, two different selections were done that yielded phage (e.g. Argo1 and Argo2) comprising the same substitution of the basic amino acid lysine for glutamic acid at residue 158 of gpE, a major surface protein of the phage λ capsid (e.g. column 20, lines 10-30). Phage Argo2 appears to also comprise a basic substitution in the major capsid protein, gpD. Merril et al teach that the phage isolated by their methods might be useful

for the treatment of microbial infections and demonstrate this capacity in a mouse model for peritonitis (e.g. column 19, lines 25-55; Figure 4).

The population of phage used in the working examples of the '093 patent can be considered as being a "phage display library" in the broad meaning that a plurality of different variants are put into a selection protocol that is dependent upon the ability of a variant to escape inactivation by the host organisms' defenses (e.g. the reticuloendothelium system) due to a different peptide sequence displayed on the capsid surface of the variant. It is noted that applicants have not specifically and explicitly defined what constitutes a "phage display library", so that a reasonably broad interpretation of the term such as that given above can be applied to the rejected claims.

The '093 patent appears to be an extension of the teachings of Merril et al (PNAS USA, Vol. 93, pages 3188-3192, April 1996). The patent further teaches that it is desirable to generate a population of fusion proteins where the fusion proteins are displayed on the surface of the phage. The patent teaches an example where the peptide sequence LARSNL is fused to the carboxyl end of one of the surface proteins of the phage. This sequence is known in the art to inhibit complement activation in both the classical and alternative pathways (e.g. columns 6-7). The patent teaches that any phage strain capable of doing direct or indirect harm to bacteria or other pathogens is contemplated for use in the methods of the invention (e.g. column 9, lines 42-48). The specification provides explicit and enabling guidance with regard to genetically engineering of both a phage whose genome is well characterized (e.g. phage λ) and phage whose genomes are not well characterized, including characterization of those peptides exposed on the surface of the phage with antibodies (e.g. Example 4).

It could be argued that the teachings of the '093 patent do not explicitly link the recombinant production of a fusion protein on the surface of the phage particle with the production of a "phage display library" that comprises a plurality of such fusion proteins displayed on the surface of such recombinant phage and that, for this reason, the '093 patent does not anticipate the rejected claims. Hence, the following rejection is made under 35 U.S.C. 103(a) over the teachings of the '093 patent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 6-8, 11, 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merril et al (U.S. Patent No. 5,811,093A; see the entire patent). **This is a new rejection.**

The teachings of Merril et al are described above and are applied as before, except:

Merril et al do not explicitly link the recombinant production of a fusion protein on the surface of the phage particle with the production of a "phage display library" that comprises a plurality of such fusion proteins displayed on the surface of such recombinant phage. Merril et al do not explicitly teach the use of a "random" phage display library that incorporates random peptide sequences as components of a fusion protein with one of the capsid surface proteins.

It would have been obvious to one of ordinary skill in the art at the time of applicants' invention to modify the teachings of the '093 patent to include the use of a library of recombinant phage displaying a plurality of different fusion proteins comprising different peptide because the patent teaches it is within the skill of the art to select stabilizing epitopes of a phage capsid protein from a plurality of variants (e.g. Argo2) and because the patent specifically teaches the use of recombinant phage displaying fusion proteins comprising epitopes derived from a number of different sources (e.g. complement antagonizing peptides, peptides derived from interleukins, cytokines, inhibitors of macrophage activating factors, etc.; see columns 6-7). One would have been motivated to do so in order to receive the expected benefit of being able to rapidly select amongst a series of displayed variants those which are most effective at inhibiting inactivation in the blood, as exemplified in the selection of mutants of phage lambda surface protein.

It would have been further obvious to the ordinarily skilled artisan at the time of the invention to utilize a library of recombinant phage displaying *random* peptide sequences as fusion proteins on the surface of the phage to identify those variants yielding prolonged half-life in the blood of a host organisms because the '093 patent already teaches the random mutagenesis of the phage capsid proteins (e.g. by propagation in mutator strains of *E. coli*) in order to provide a larger pool of variants from which to select those variants conferring prolonged circulation in the blood of a host organism. One would have been motivated to do so in order to receive the expected benefit, as exemplified by Merril et al for the random variants of the wildtype phage capsid proteins, of obtaining a larger pool of variants from which to select those mutants conferring enhanced stability. Absent any evidence to the contrary, there would have been a

reasonable expectation of success in incorporating fusion proteins comprising random peptide sequences into the phage display methods taught by the '093 patent.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Merril et al (PNAS USA, Vol. 93, pages 3188-3192, April 1996; see the entire reference) or Merril et al (U.S. Patent No. 5,811,093A; see the entire patent) in view of the 1997 Novagen Catalog (Novagen, Inc. pages 24-26 of the 1997 catalog). **This is a new rejection.**

The teachings of each of the Merril et al references are described above and are applied as before, except:

Neither of the Merril et al references explicitly teach the use of T7 phage in their methods of selecting for phage resistant to inactivation by components of the blood of a host organism.

The 1997 Novagen catalog provides teachings concerning a "T7Select" phage display system that was well known and used in the art at the time of the instant invention (see pages 24-26 of the catalog). In particular, the catalog teaches several advantages of the T7 system, including ease of growth and high copy number for displayed peptides (e.g. the table labeled "Advantages" on page 24).

It would have been obvious to the one of ordinary skill in the art at the time of the invention to modify the teachings of either of the Merril et al references to include the T7 phage display system taught and sold by Novagen because both of the Merril et al references teach it is within the skill of the art to use a population of phage displaying a plurality of variations of the coat polypeptides to select variants that demonstrate a resistance to inactivation in the blood of a host organism. It would have been obvious to make such a modification in order to receive any

of the expected benefits recited in the teachings of the Promega cagalog with regard to using T7 phage display systems. In addition, or alternatively, one could reasonably expect to select for phage having different display characteristics than the lambda phage exemplified in the teachings of the Merril et al references and/or a different range of target bacterial cells capable of infection by the phage. Absent any evidence to the contrary, there would have been a reasonable expectation of success in modifying the teachings of either of the Merril et al references to include the T7Select system taught by the Novagen catalog.

Conclusion

No claims are allowed. This action is not final. Claim 5 is objected to as being dependent upon a rejected claim, but would be allowable if rewritten in independent form comprising each of the limitations of the claim upon which it is currently dependent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
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GERRY LEFFERS
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